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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/718,717	11/22/00	JAKOBOVITS A	APHX-001CON2

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EXAMINER	
MCKELVEY, T	
ART UNIT	**PAPER NUMBER**
1636	6

DATE MAILED: 09/07/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/718,717	Applicant(s) JOKOBOVITS ET AL.	
	Examiner Terry Mckelvey	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *8 and 13-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

Applicant's election with traverse of Group I, claims 1-7 and 9-12 in Paper No. 4, filed 6/28/01 is acknowledged. The traversal is on the ground(s) that the claims of the two groups are very much related to each other in that a common element in all of the claims is the method employed to produce the cell, thus there is no undue burden to examine all of the claims. In other words, all of the relevant prior art for Group II would be found in the search for Group I because both groups require the practice of the claimed method of Group I. This is not found persuasive because, as it was set forth in the previous communication, the cell of Group II reads on cells produced by another method, such as by isolation of cells with a natural deletion, such as cells having chromosomal breakpoint mutations. Although the cells of Group II depend on the method of Group I, because cells produced by another method which results in cells having a large deletion would have the same structure, art describing cells produced by the other methods has to be searched in different patent and non-patent searches, independent of searching for the method of Group I.

The applicant also pointed out that both Groups were searched together in the prosecution that matured into U.S. Patent No. 5,998,209, and as such, any search now performed can build on the search already performed in the parent and thus searching those groups together should not impose an undue burden. It is correct that both groups were examined together. In fact, it was that examination that demonstrated to the examiner that there is an undue burden in examining both groups together. Also, because of the rapid increase in the volume of the patent and non-patent literature in the biotechnological arts, a full search for the relevant art for both groups would require search and consideration of a large amount of art that was not previously available and thus would require essentially a completely new search, not merely a slight update of a previous search.

The requirement is still deemed proper and is therefore made FINAL.

Claims 8 and 13-15 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 4.

Priority

This application filed under former 37 CFR 1.60 lacks the necessary reference to the prior application. A statement reading "This is a continuation of Application No. 09/348,747, filed 7/6/99, abandoned, which is a continuation of 08/808,139, filed 4/16/97, now U.S. Patent No. 5,998,209, which is a continuation of 08/426,555, filed 4/21/95, abandoned." should be entered following the title of the invention or as the first sentence of the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 9-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a mammalian cell having about 55 kb deletion, does not reasonably provide enablement for making a deletion in the entire range of 15 kb to 3000 kb. The specification does not enable any person skilled in the art to which it pertains, or with which it

is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are drawn to a method for obtaining a mammalian cell containing a genomic deletion of 15-3000 kb by homologous recombination with a construct comprising two regions of sequences which are homologous to the 5' and 3' flanking sequences of the region to be deleted and a mammalian cell prepared by such a method.

In order to practice the invention, one of skill must make a construct containing 5' and 3' regions of the wild-type gene and successfully introduce the construct into a mammalian cell and obtain by selection a homologous construct. In order to achieve this goal, one must also include the following intervening steps, that is a) identifying cells containing the deletion by selecting cells containing a selectable marker present in the construct, and b) recovering cells containing the deletion.

The state of the prior art was that a deletion up to 19.2 kb was made in ES cells at the hprt locus, occurring at the same frequency as smaller deletions (Zhang et al (AX), abstract). This reference also suggested that "If this observation can be generalized, a wide spectrum of genomic deletions can be made in ES cells which may facilitate the analysis of gene function." (pages 2409-2410). Thus, from the data in the reference, that large deletions are detected as frequently as smaller deletions

and that the result might be generalized, it suggests that larger deletions may be possible. However, a reference published a year and a half later, Ramirez-Solis et al (AP), teaches that "Small deletions (20 kb) have been generated in embryonic stem (ES) cells by conventional gene targeting, but the construction of larger deletions, inversions or duplications has not been possible." (page 720, paragraph 1). Thus, although Zhang et al suggest that a broad spectrum of deletions may be possible, Ramirez-Solis et al teach that a year and a half later, no larger deletions were made. Thus, these references show or suggest that smaller deletions, about 19 kb are possible, but larger deletions are unpredictable and the art fails to provide guidance or working examples of deletions greater than about 19 kb.

The guidance presented in the specification is limited to a construct comprising two regions of sequences which are homologous to the 5' and 3' flanking sequences of the region to be deleted in the wild-type locus, identifying cells containing the deletion by selecting cells containing a selectable marker present in the construct, and recovering the cells containing the deletion in order to obtain a mammalian cell containing a genomic deletion. The specification gives limited guidance to making a broad range of deletions, but this guidance is speculative (and thus limited) because it is based upon a single working example of making a deletion in the claimed range, i.e. deletion of 55 kb

of the mouse hprt gene in embryonic stem (ES) cells, although the art teaches the unpredictability of making large deletions.

The relative skill of those in the art is high.

The claims are broad in that a very wide range of deletions is being claimed: 50 kb to 3000 kb.

Therefore, in order to practice the full scope of the claimed invention, the skilled artisan would have to envision constructs to be used in the claimed homologous recombination method, test them in the claimed homologous recombination method, and if the method failed to isolate cells having deletions other than about 50-55 kb, envision modifications to the vectors or method, test the modifications, and repeat the unpredictable experimentation until cells containing deletions other than about 50-55 kb are isolated. Because of the state of the prior art, in which no larger than 20 kb deletions were made, the unpredictability in the art of generating large, 20 kb+ deletions, taught in the art even after the filing date of the instant application, the lack of guidance in either the art or the specification for making such large deletions (except for about a 50-55 kb deletion), and the lack of working examples (except for about a 50-55 kb deletion) in either the art or the specification (for deletions greater than 19.2 kb), it would require much unpredictable experimentation to practice the full

scope of the invention given the failure in the prior art. This experimentation would be undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 and 9-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to claims 1, etc, the claims fail to recite positive process steps which clearly relate to the preamble, making the claims unclear because it is unclear whether the claimed method is what the preamble states or what the method steps actually result in. The preamble recites "obtaining a mammalian cell...", while the final method step is one of "introducing a construct...". A correlation step or a "thereby obtaining..." should be added.

With regard to claims 3, 4, etc, there is no positive antecedent basis for "said target locus".

With regard to claims 4-5, the use of "the MHC class I (or class II) locus renders the claims vague and indefinite because MHC genes are found in several loci.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 7, and 9-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al (AX).

The claimed invention is a method of obtaining a mammalian cell containing a deletion greater than 15 kb by homologous recombination. Said method, with the target locus being the HPRT locus, is also claimed.

Zhang et al teach a method of targeting genomic deletions by homologous recombination of vectors that contain the same 5' vector arm, and 3' vector arms homologous to different positions in the gene (abstract; page 2405). This reference also teaches the identification and recovery of cells containing a deletion by selection using a selectable marker (neo resistance) (page 2405,

column 1). Deletions of the hprt gene ranging from 3.0 to 19.2 kb were obtained in ES cells (page 2405, paragraph 1 under "Results"). The reference also teaches using the method with embryonic stem cells, which are mammalian cells (Table 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 7 and 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (AX) in view of Kucherlapati et al (AA).

The claimed invention is a method of obtaining a mammalian cell containing a deletion greater than 15 kb or 15-3000 kb by homologous recombination. Said method, with the target locus being the HPRT locus, MHC class I, or class II locus is also claimed.

Zhang et al teach a method of targeting genomic deletions by homologous recombination of vectors that contain the same 5' vector arm, and 3' vector arms homologous to different positions in the gene (abstract; page 2405). This reference also teaches the identification and recovery of cells containing a deletion by selection using a selectable marker (neo resistance) (page 2405, column 1). Zhang et al teach that for genetic analysis, it is desirable to delete major portions of a gene, particularly when a genetic region is large or complex (page 2404, paragraph 2). Deletions of the hprt gene ranging from 3.0 to 19.2 kb were obtained in ES cells (page 2405, paragraph 1 under "Results"). All of the different sizes of deletions tested occurred at comparable frequencies. Zhang et al teach that "In summary, the experiments presented here demonstrated that deletions as large as 19.2 kb could be made at the hprt locus in mouse ES cells. The frequency with which a targeted deletion could be generated

was comparable to that of smaller (11.5- or 3-kb) deletions or a conventional replacement. If this observation can be generalized, a wide spectrum of genomic deletions can be made in ES cells which may facilitate the analysis of gene function." (page 2409, last paragraph - page 2410, paragraph 1). The reference also teaches using the method with embryonic stem cells, which are mammalian cells (Table 1).

Zhang et al do not specifically teach deletion of a target locus which is the MHC class I or class II locus.

Kucherlapati et al teach a method of inactivating MHC class I genes by homologous recombination between the endogenous wild-type genes and a clone vector containing the MHC class I gene and flanking sequences using ES cells (columns 3-5). This reference also teaches that substantially the same procedures will suffice for MHC Class II genes (column 5).

It would have been obvious to one of skill in the art at the time the invention was made to use the method of making large deletions (up to about 19.2 kb) taught by Zhang et al in making deletions in any other genetic locus, such as MHC class I or II (such as that taught by Kucherlapati et al) because Zhang et al teach that it is within the ordinary skill in the art to make deletions up to about 19 kb and specifically teaches that for genetic analysis, it is desirable to delete major portions of a gene, particularly when a genetic region is large or complex.

The MHC class I and class II loci are and were well known in the art to be such loci, as shown by the teachings of Kucherlapati et al. One would have been motivated to do so for the expected benefit of making large deletions for genetic analysis, as taught by Zhang et al. Based upon the teachings of the cited references and absent evidence to the contrary, there would have been a reasonable expectation of success, that using the method of Zhang et al, one of ordinary skill in the art would have been able to make large deletions, up to about 19.2 kb, in other loci known in the art, such as the MHC class I and class II loci taught by Kucherlapati et al.

Claims 1-3, 6-7 and 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (AX) in view of Kucherlapati et al (AD).

The claimed invention is a method of obtaining a mammalian cell containing a deletion greater than 15 kb or 15-3000 kb by homologous recombination. Said method, with the target locus being the HPRT locus or immunoglobin locus is also claimed.

Zhang et al teach a method of targeting genomic deletions by homologous recombination of vectors that contain the same 5' vector arm, and 3' vector arms homologous to different positions in the gene (abstract; page 2405). This reference also teaches

the identification and recovery of cells containing a deletion by selection using a selectable marker (neo resistance) (page 2405, column 1). Zhang et al teach that for genetic analysis, it is desirable to delete major portions of a gene, particularly when a genetic region is large or complex (page 2404, paragraph 2). Deletions of the hprt gene ranging from 3.0 to 19.2 kb were obtained in ES cells (page 2405, paragraph 1 under "Results"). All of the different sizes of deletions tested occurred at comparable frequencies. Zhang et al teach that "In summary, the experiments presented here demonstrated that deletions as large as 19.2 kb could be made at the hprt locus in mouse ES cells. The frequency with which a targeted deletion could be generated was comparable to that of smaller (11.5- or 3-kb) deletions or a conventional replacement. If this observation can be generalized, a wide spectrum of genomic deletions can be made in ES cells which may facilitate the analysis of gene function." (page 2409, last paragraph - page 2410, paragraph 1). The reference teaches use of embryonic stem cells, which are mammalian cells, in the method (Table 1).

Zhang et al do not specifically teach deletion of a target locus which is the immunoglobin locus.

Kucherlapati et al teach a method of inactivating mouse immunoglobin (Ig) genes in ES cells by homologous recombination between the endogenous wild-type genes and a clone vector

containing the Ig gene and flanking sequences and use of ES cells in the method (pages 16-22).

It would have been obvious to one of skill in the art at the time the invention was made to use the method of making large deletions (up to about 19.2 kb) taught by Zhang et al in making deletions in any other genetic locus, such as the immunoglobin locus taught by Kucherlapati et al because Zhang et al teach that it is within the ordinary skill in the art to make deletions up to about 19 kb and specifically teaches that for genetic analysis, it is desirable to delete major portions of a gene, particularly when a genetic region is large or complex. The immunoglobin loci is and was well known in the art to be such loci, as shown by the teachings of Kucherlapati et al. One would have been motivated to do so for the expected benefit of making large deletions for genetic analysis, as taught by Zhang et al. Based upon the teachings of the cited references and absent evidence to the contrary, there would have been a reasonable expectation of success, that using the method of Zhang et al, one of ordinary skill in the art would have been able to make large deletions, up to about 19.2 kb, in other loci known in the art, such as the Ig locus taught by Kucherlapati et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7 and 9-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 8, 12, 15-18 of U.S. Patent No. 5,998,209. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons.

The claims of '209 are drawn to a method for obtaining mammalian cells comprising a genomic deletion of about 55 kb and a method for preparing mammalian cells deficient in the HPRT locus. The instant claims are drawn to a method for obtaining mammalian cells comprising a genomic deletion of about 50-55 kb, or 50-3000 kb and method for preparing mammalian cells deficient

in the HPRT locus, which are broader in scope and totally encompassing the '209 methods, and thus are obvious because they are the same invention, but claimed in a broader fashion. Thus, the instant claims, if allowed, would result in the improper timewise extension of the patent protection of the '209 methods, in addition to providing patent protection to the methods and cells not encompassed by the claims of '209 (i.e., drawn to methods for and cells containing deletions which are not about 55 kb). Also, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the '209 patent, then two different assignees would hold a patent that covers the claimed methods of '209, and thus improperly there would be possible harassment by multiple assignees.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original

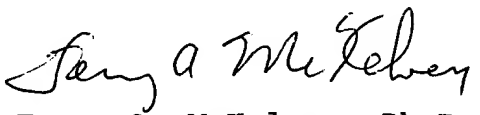
signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning missing attachments or other minor formalities of this communication should be directed to the patent analyst, Zeta Adams, whose telephone number is (703) 305-3291.

Any inquiry concerning rejections or other major issues in this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Dr. Robert Schwartzman, can be reached on (703) 308-7307.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

September 7, 2001